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TITLE: A Role for TACI in Prostate Neoplasia

PRINCIPAL INVESTIGATOR: Gotz-Ulrich Von Bulow, Ph.D.

CONTRACTING ORGANIZATION: Indiana University School of Medicine
Indianapolis, IN 46202

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Gotz-Ulrich Von Bulow, Ph.D.

E-Mail: gvonbulo@iupui.edu

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Indiana University School of Medicine
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13. SUPPLEMENTARY NOTES

14. ABSTRACT: This research study proposed that TNF-family growth factors, BAFF and APRIL play a role in prostate cancer. Our hypothesis proposed that APRIL provides a proliferative signal to normal prostate epithelial cells by means of an unknown receptor. We postulated that TACI is an antagonist receptor which functions to regulate APRIL-mediated proliferation of cells by inducing apoptosis and thereby maintaining the normal glandular structure. The loss of TACI expression in prostate cells therefore conceivably results in an imbalance in homeostasis resulting in the aberrant accumulation of cells which become susceptible to transformation. Our hypothesis anticipated that the addition of APRIL would enhance cell growth whereas the addition of TACI-Ig would either reduce cell growth or induce apoptosis. This did not happen and we did not see an significant changes in the relative numbers of hyperdiploid cells as determined by propidium iodide flow cytometry. Because of the negative results, the study was terminated early and the grant relinquished. Dr. Von Bulow no longer works for Indiana University.

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Prostate Cancer

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Table of Contents

INDIANA UNIVERSITY

SCHOOL OF MEDICINE

OFFICE OF THE CHAIRMAN/SCIENTIFIC DIRECTOR

CHAIRMAN

DEPARTMENT OF MICROBIOLOGY AND IMMUNOLOGY

MS 420
635 North Barnhill Drive
Indianapolis, Indiana
46202-5120

SCIENTIFIC DIRECTOR

WALTHER ONCOLOGY CENTER

R2 302
950 West Walnut Street
Indianapolis, Indiana
46202-5181

317-274-7501
317-274-7502
Fax: 317-274-7592

June 17, 2008

Brian E. Martin
Contracting Officer
US Army Medical Research Acquisition Activity
ATTN: MCMR-AAA-R
820 Chandler Street
Fort Detrick MD 21702-5014
Pat Connors@us.army.mil

Dear Mr. Martin:

On behalf of Indiana University and Dr. Gotz-Ulrich Von Bulow who is no longer employed by Indiana University, I have completed the missing annual report for the period 12/15/04-12/14/05, the final progress report and the Animal Use report for this grant. These reports were generated utilizing the data available from the report Dr. Von Bulow completed one year ago which he believed to be the final report when the grant was relinquished. Dr. Von Bulow is no longer available to complete the reports and I have completed them as Chairman of his department.

Sincerely Yours,

Hal E. Broxmeyer

Hal E. Broxmeyer, Ph.D.
Distinguished Professor,
Chairman & Mary Margaret Walther
Professor of Microbiology/Immunology,
Professor of Medicine,
Scientific Director of the Walther Oncology Center

Missing Annual Report 12/4/04-12/14/05

Introduction

The goal of this grant was to gain insight into the molecular basis of prostate cancer. Preliminary evidence suggested that the taci gene is expressed in normal prostate tissues, but not in prostate tumor cells. We had proposed the APRIL provides a proliferative signal to normal prostate epithelial cells by means of an unknown receptor.

Body

To determine the role of APRIL and TACI in prostate tumor growth, we cultured LNCaP, PC3 and DU145 prostate cancer cell lines and titrated the effects of recombinant APRIL and TACL-Ig on cell growth as determined by MTT assay, DNA content of cells and Annexin V binding assays;

Reportable Outcomes

(a) According to our hypothesis we anticipated that the addition of recombinant APRil would enhance cell growth whereas the addition of TACi-IL would either reduce cell growth or induce apoptosis. This did not happen and for all four cell lines tested we did not see any significant changes in relative cell number (ad determined by MTT reduction), nor did we see any significant changes in the relative numbers of hyperdiploid cells as determined by propidium iodide flow cytometry. These experiments were repeated several times with similar results. To overcome the possibility that the cells were already maximally stimulated in the presence off fetal calf serum, we repeated the MTT experiments in either serum-free conditions, or in medium with 1% fetal calf serum. Although the MTT values were reduced overall, there was no significant difference observed when titrating in either APRIL or TACI-Ig. We included the titration with BAFF since it is also a TACI ligand, but similar negative results were obtained with this cytokine. When performing the apoptosis assays with propidium iodide and annexin V staining, we encountered a pitfall in that we were not able to separate the cells from the monolayer into individual cells for flow cytometry using EDTA or trypsin without affecting the viability of the cells (and thereby propidium iodide staining). Overall these types of experiments were not very reproducible and were therefore abandoned as unreliable.

Conclusions

We will not perform the experiments to determine the effect of systemic TACI-Ig administration on the growth of LNCaP cells in nude mice because of our negative results. We will continue to look at growth characteristics in the presence of doxcycyclin when compared with the parental cell lines.

References: None

Appendices: None